Understanding the Rules of Life: Predicting Phenotype

April 25, 2017

Boston University Office of the Vice President and Associate Provost for Research

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ATGL and Longevity

Konstantin Kandror

Professor

Biochemistry
MED

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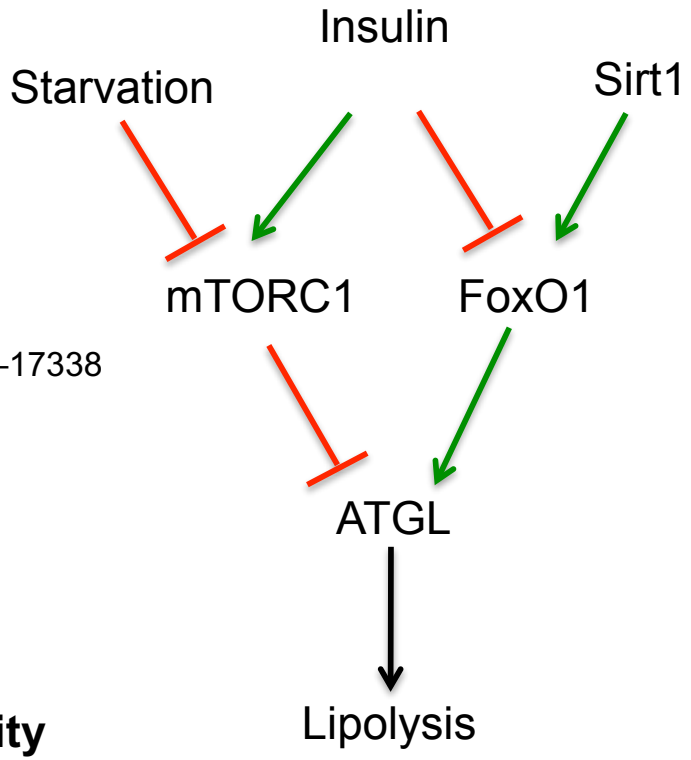
Insulin regulates the expression of the rate-limiting lipolytic enzyme, ATGL



Diabetes, 2010, 59, 775-781
MCB, 2013, 33, 3659-3666
J.Biol.Chem., 2015, 290, 17331–17338

J.Biol.Chem., 2009, 284,13296-13300
J.Lipid Res., 2011, 52, 1693-1701

Potential links to longevity

1. Calorie restriction
2. Inhibition of IIS
(traced down to Daf-16 and dFoxO)
3. Rapamycin and genetic manipulations
with the mTORC1 pathway
4. Sir2/Sirt1

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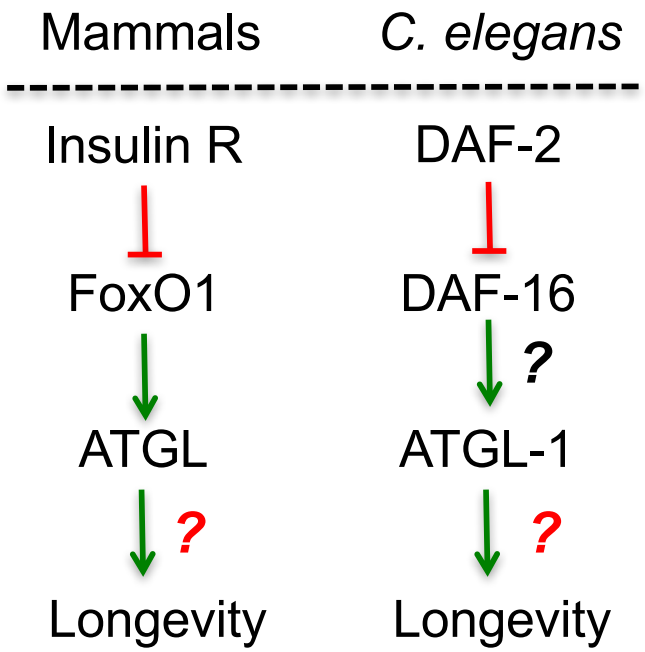
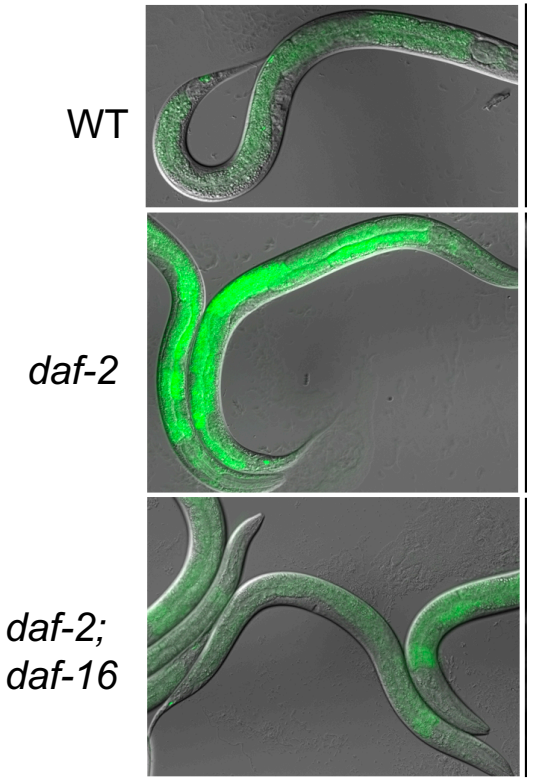
ATGL-1::GFP expression in *C. elegans*





Larval stage 4
200x magnification
450 ms exposure

FUNDING: NIH, ADA

With Alla Grishok

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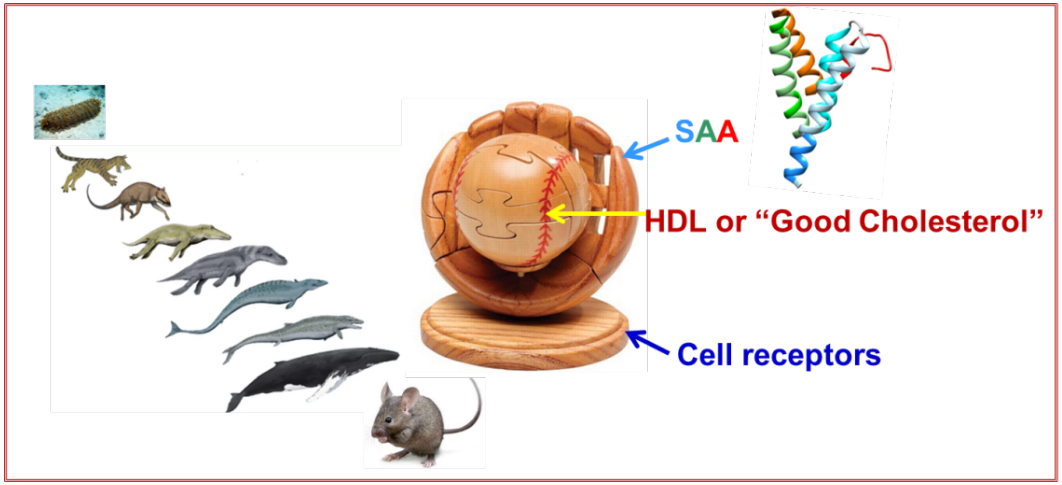
Serum Amyloid A: An Acute-Phase Protein in Search of Ligands



Olga Gursky

Professor

Physiology & Biophysics
MED

Nicholas Frame, Shobini Jayaraman, Donald Gantz

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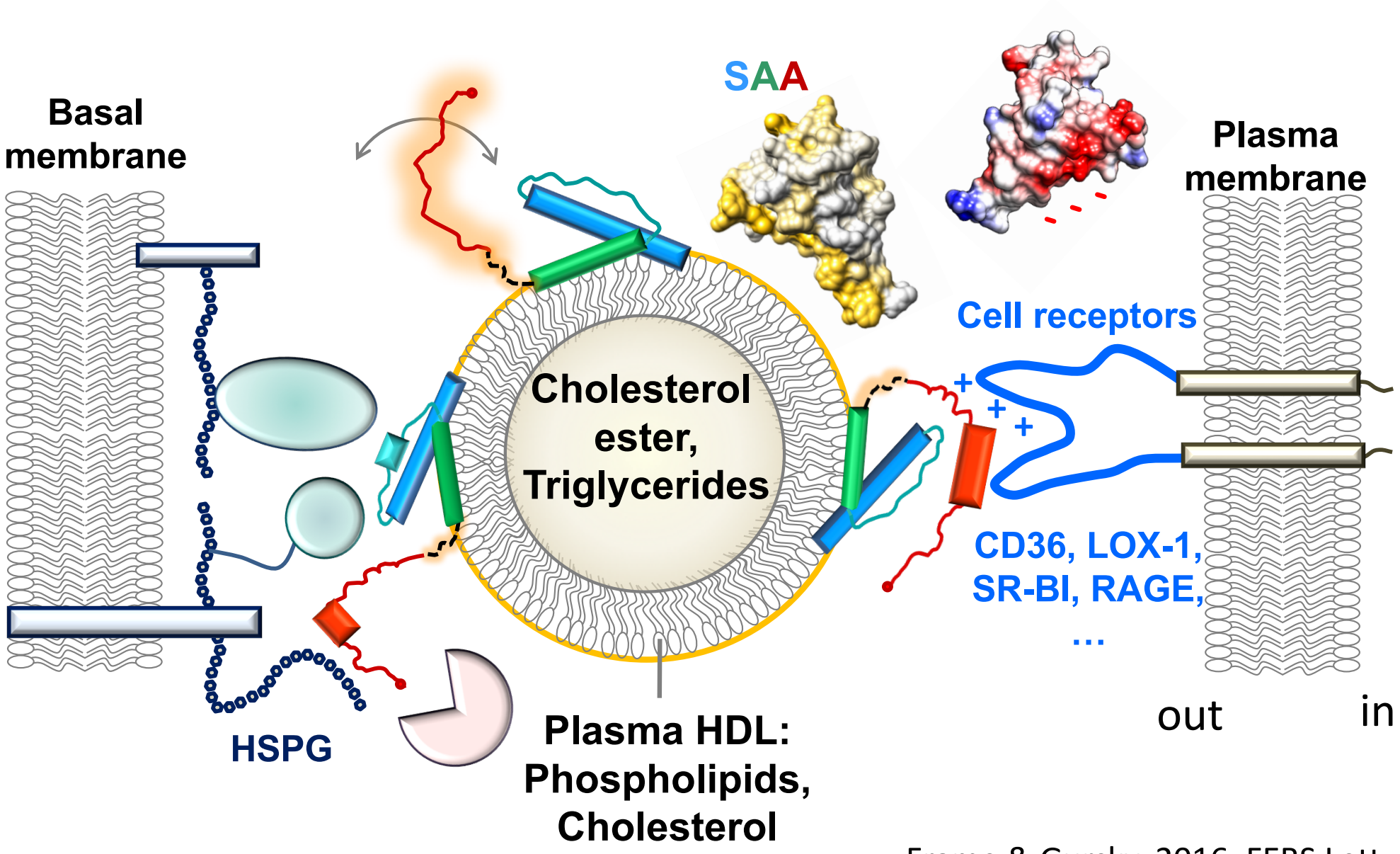
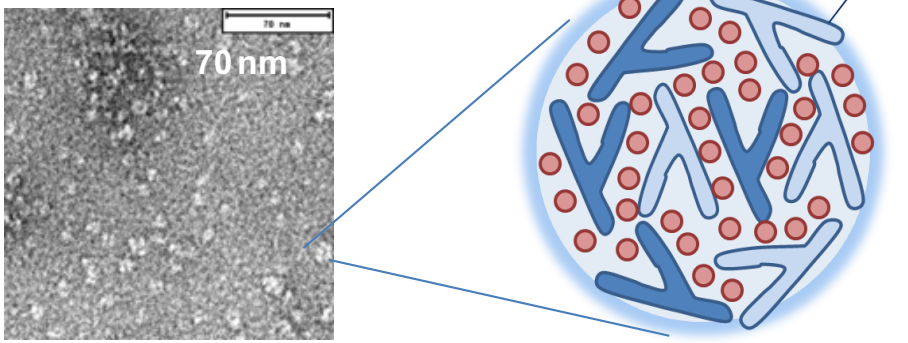
SAA on acute-phase HDL: an intrinsically disordered protein hub

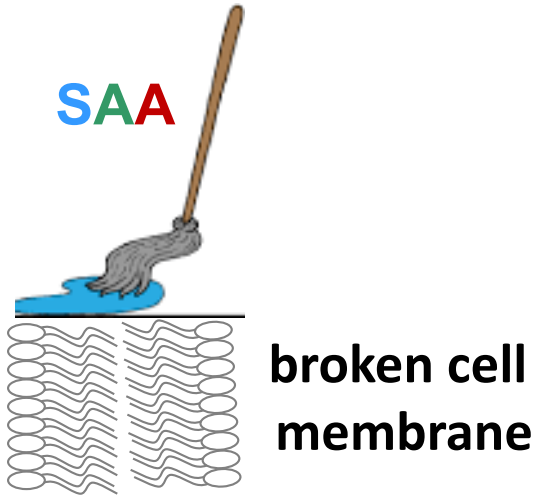


Frame & Gursky, 2016, FEBS Lett

A new function for an ancient protein: A "molecular mop"

- **SAA can also generate lipoproteins *de novo* by solubilizing lipid bilayers in a spontaneous energy (ATP)-independent process.**
- **This process is relevant to inflammation and injury when membranes of dead cells require rapid removal but ABC transporters do not work.**





- **SAA re-packs lipids into nanopartocles that are taken up by receptors (CD36, LOX-1, RAGE, etc.) on various cells and used for tissue repair.**
- **The ability of SAA to rapidly clear cell debris probably represents the primordial function of this ancient acute-phase reactant.**

Mechanisms Driving Inflammation in Human Obesity and Type 2 Diabetes

Barbara Nikolajczyk

Associate Professor

Microbiology
MED

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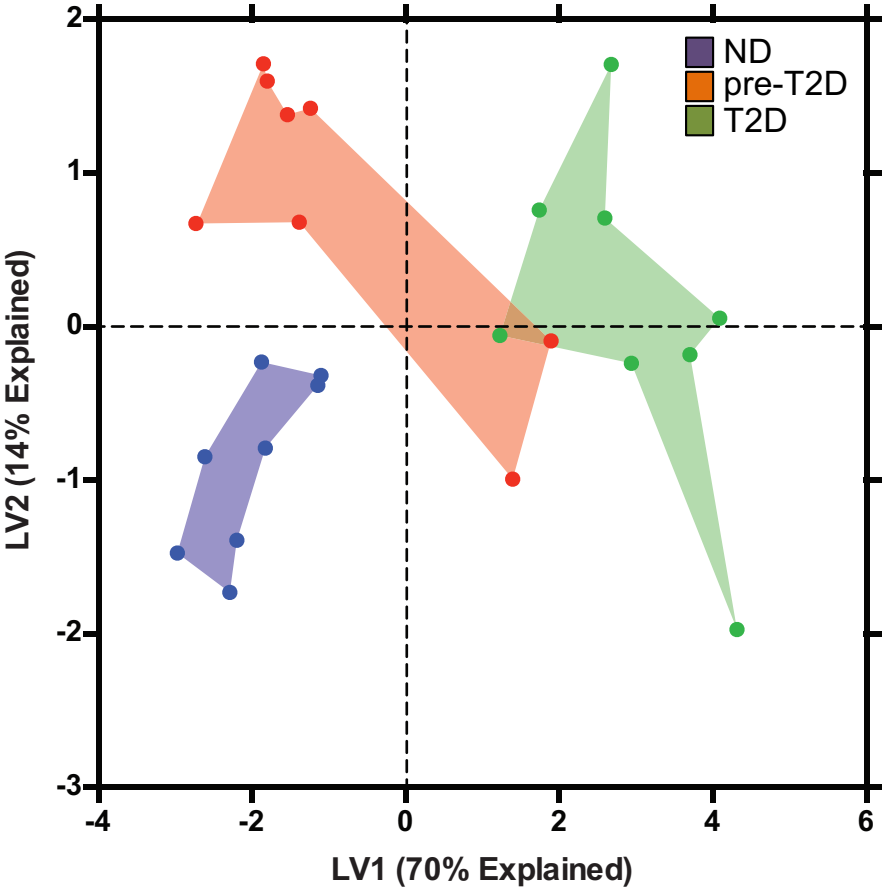
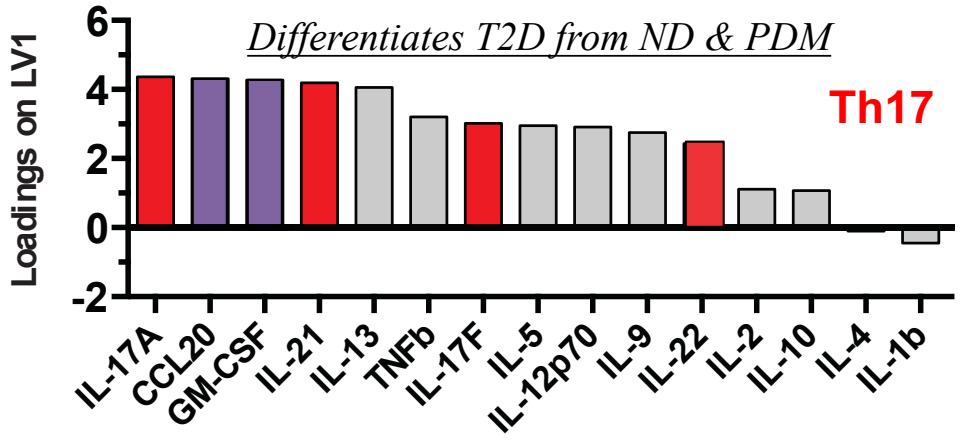
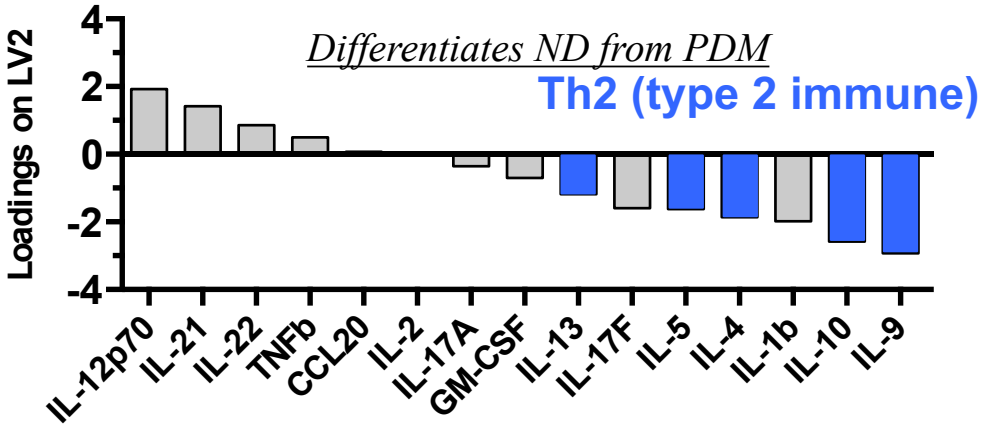
The Definition of "Inflammation" Dynamically changes during the Development of Type 2 Diabetes







Prediction

T cell cytokines can be used to accurately determine multiple disease states

(Calibration Accuracy = 83%, Cross-Validation Accuracy = 75%)

Interpretation

Th17 signature cytokines are unique to classifying T2D subjects, while Th2 cytokines may differentiate ND from pre-T2D; different T cell subsets dominate different stages of disease progression

Massachusetts Institute of Technology

Ip et al. Obesity, 2016

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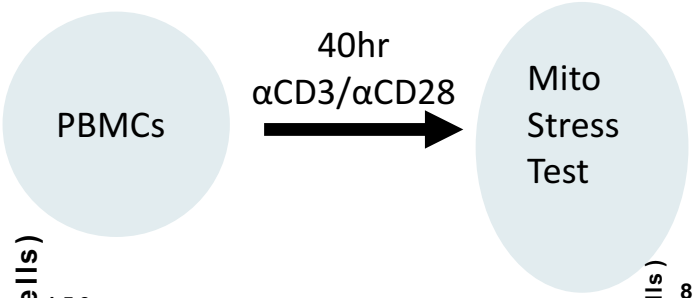
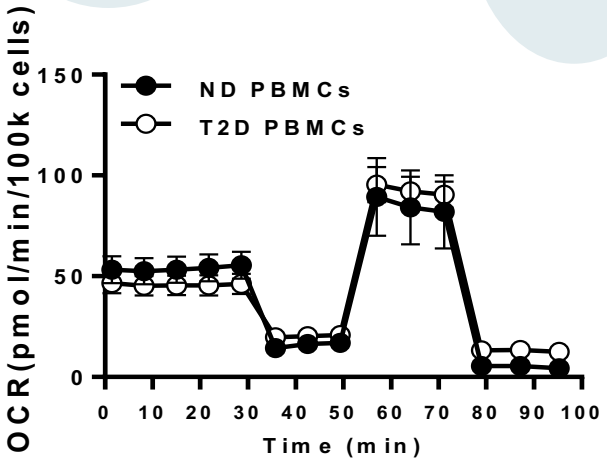
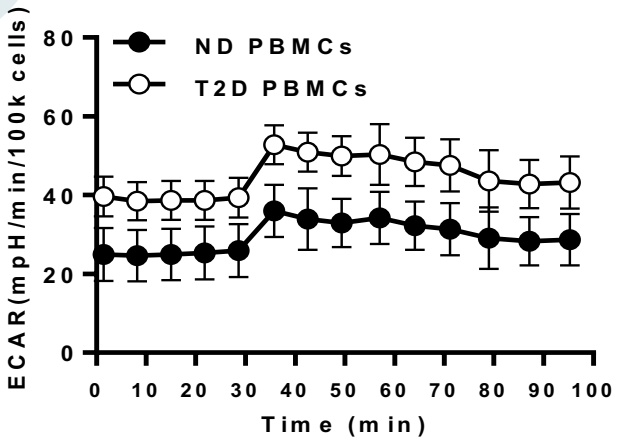
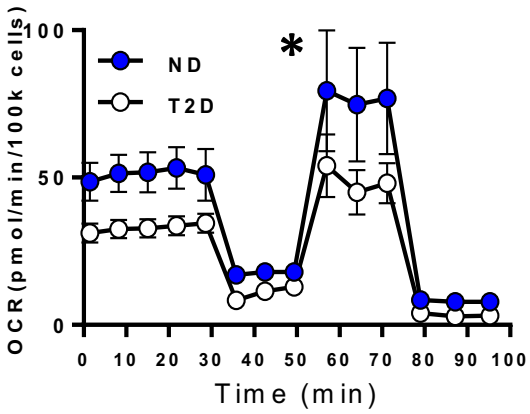
PBMCs from T2D are more Glycolytic than PBMCs from ND



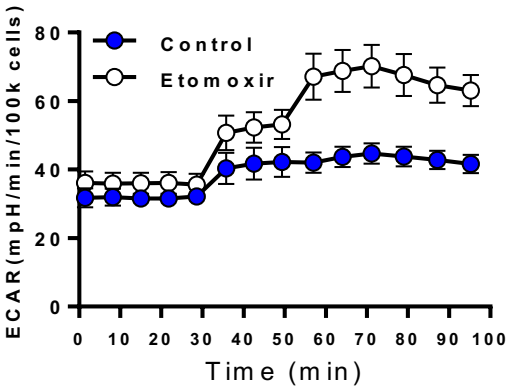




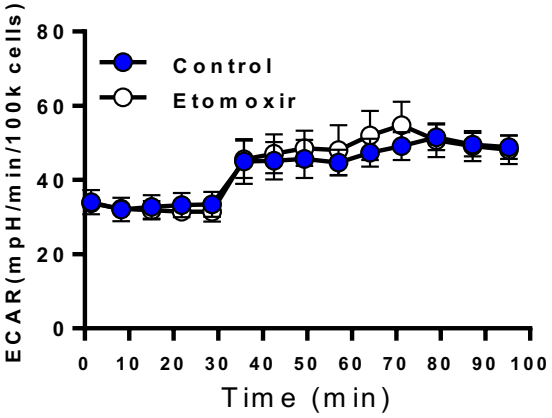
no glucose



ND



T2D



N=4, *N=2 for T2D in etomoxir graph only

Does glycolysis drive the Th17 signature?

Nicholas et al., unpublished

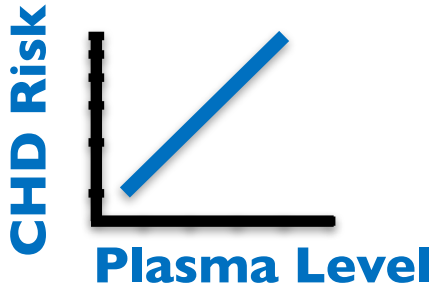
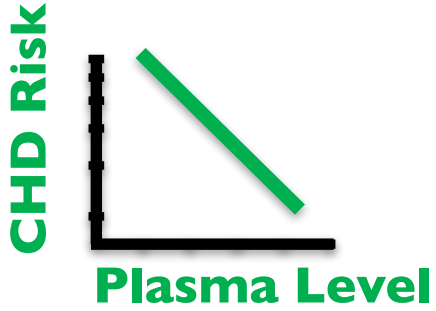
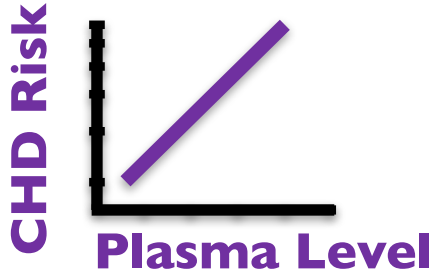
Leveraging Human Genetic Variation to Predict the Effect of Plasma Lipids on Coronary Heart Disease

Gina M. Peloso
Assistant Professor

Biostatistics
SPH

BOSTON UNIVERSITY

Lipid pathways and Coronary Heart Disease (CHD)

	Epidemiology	Genetics	Therapy
LDL ✓		***LDLR*** ***PCSK9*** ***NPC1L1***	**Statins** **PCSK9 Abs** **Ezetimibe**
HDL ✗		***Common variants:*** ***no effect on CHD*** ***Rare variants:*** ***no effect on CHD*** Voight*, Peloso*, et al. *Lancet* (2012)	 **Failed**
TG ✓		***Common variants*** ***effect on CHD*** Do, et al. *Nature Genetics* (2013) ***Rare variants:*** ***APOC3, APOA5, LPL*** Crosby*, Peloso*, et al. *N Engl J Med* (2014) Do, et al. *Nature* (2015)	?

Leveraging Human Genetic Variation to Predict the Effect of Plasma Lipids on Coronary Heart Disease

- Genetic variation can be leveraged to predict the effects of biomarkers on disease
- Naturally-occurring null mutations are valuable in determining the effect of a therapeutic target

Metabolic Disease: Knockout Mice for Investigation of Disease

Dean R. Tolan

Professor

Biology
CAS

Boston University Office of the Vice President and Associate Provost for Research

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FRUCTOSE THE ONLY NUTRIENT THAT CAUSES ENERGY DEPLETION

Fructose

ATP

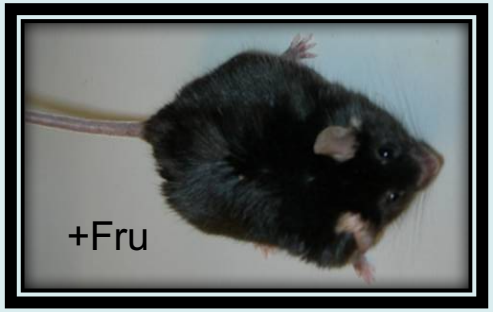
KHK

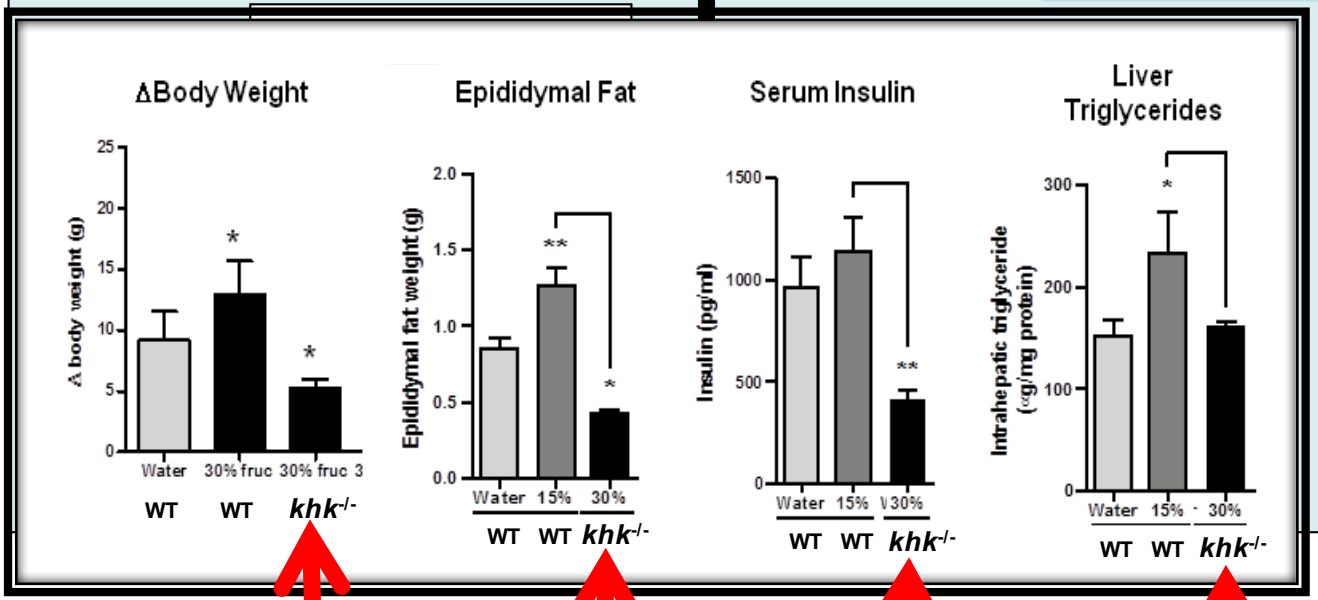
AMP

Uric acid

Fructose 1-P

ENERGY DEPLETION PATHWAY





Ishimoto T et al. 2012 *PNAS* *109:4320*

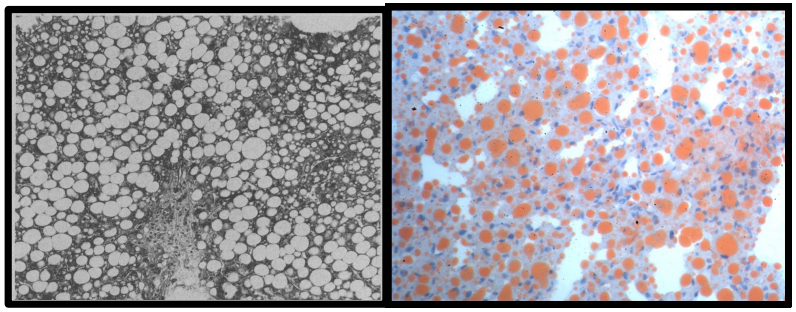
Hereditary Fructose Intolerance (HFI)

- One of the thousands of a single-gene disorders collectively termed Inborn Errors of Metabolism – Carbohydrate metabolism
- Intake of fructose results liver failure and Death

Giltzelmann *et al*., 1995

The *aldoB*$^{-/-}$ mouse

WT Knockout

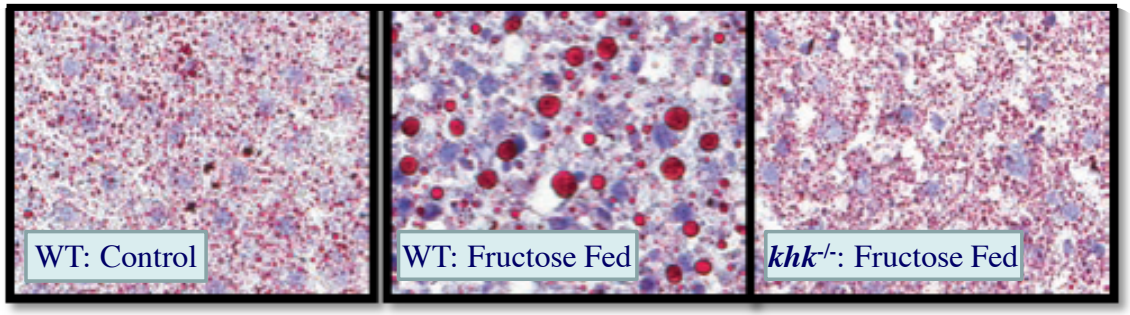


HFI Child (3 yo) after 3 wk of no fructose

aldoB$^{-/-}$ mouse (8 wo) after 1 wk of 40% fructose exposure

Liver pathology of persistent fatty liver is similar to that seen in HFI

Blocking Fructose Metabolism Prevents Fatty Liver



Acknowledgement:
Drs. Rick Johnson & Miguel Lanaspa at Univ. Colo. Denver Med. Cntr.

Obesity and Region Specific Gene Expression in Brain and Genomics of Alzheimer's Disease

Anita L. DeStefano

Professor

Biostatistics, SPH, and Neurology, MED

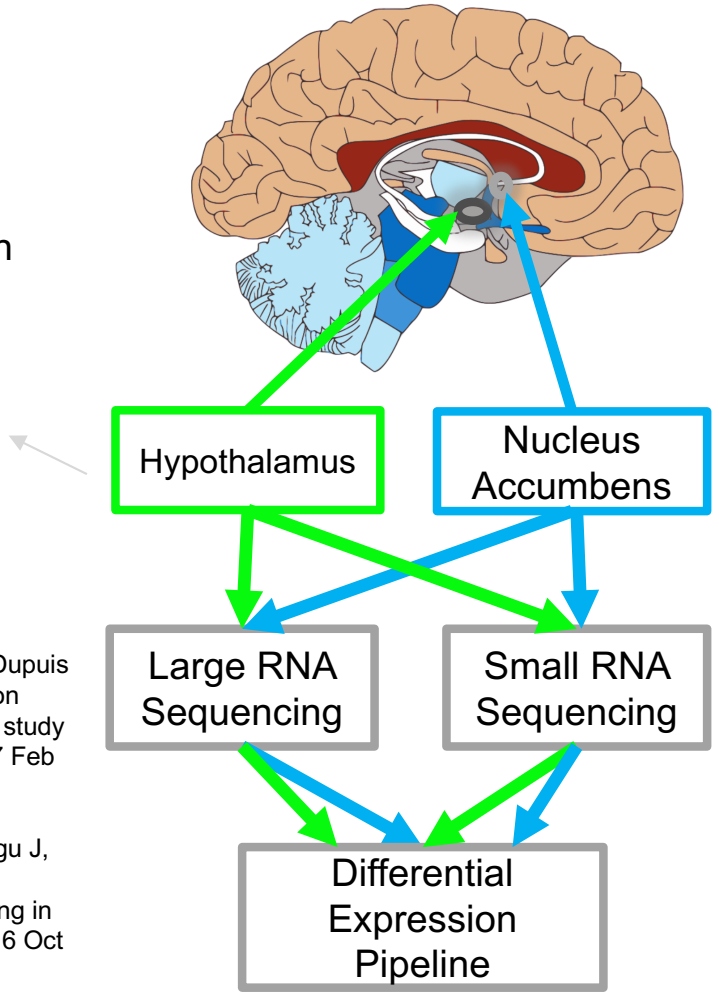
Associate Director | BU Genome Science Institute; and
Director | Graduate Certificate Program in Statistical Genetics

Neuroendocrine Control of Obesity

Framingham Heart Study
Religious Orders Study
Memory and Aging Project

Longitudinal cohort studies with brain donor programs

Tyrosinase Related Protein ???



Obese and Control post mortem brain tissue from two regions

MT-RNR1 ???
Mitocondrially encoded 12S rRNA – MOTS-c protein associated with insulin sensitivity and obesity

Choi SH, Labadorf AT, Myers RH, Lunetta KL, Dupuis J, DeStefano AL. Evaluation of logistic regression models and effect of covariates for case-control study in RNA-Seq analysis. BMC Bioinformatics. 2017 Feb 06; 18(1):91. PMID: 28166718.

Wake C, Labadorf A, Dumitriu A, Hoss AG, Bregu J, Albrecht KH, DeStefano AL, Myers RH. Novel microRNA discovery using small RNA sequencing in post-mortem human brain. BMC Genomics. 2016 Oct 04; 17(1):776. PMID: 27716130.

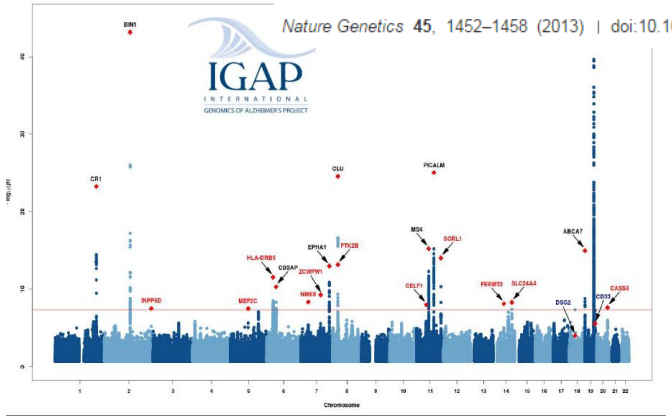
Collaborators:
Rick Myers, Sudha Seshadri, David Bennett, Thor Stein
Chris Wake (graduate student)

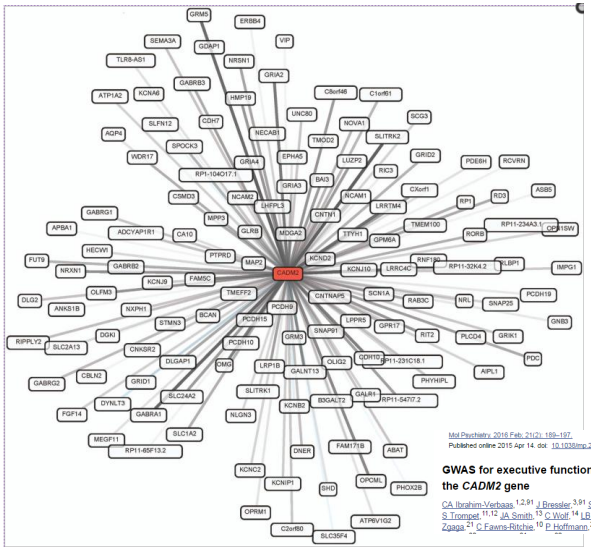
Alzheimer Disease Sequencing Project (ADSP)

Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease

Jean-Charles Lambert, Carla A Ibrahim-Verbaas, Denise Harold, Adam C Naj, Rebecca Sims, Céline Bellenguez, Gyungah Jun, Anita L DeStefano, Joshua C Bis, Gary W Beecham, Benjamin Grenier-Boley, Giancarlo Russo, Tricia A Thornton-Wells, Nicola Jones, Albert V Smith, Vincent Chouraki, Charlene Thomas, M Arfan Ikram, Diana Zelenika, Badri N Vardarajan, Yoichiro Kamatani, Chiao-Feng Lin, Amy Gerrish, Helena Schmidt, Brian Kunkle + *et al.*

Nature Genetics **45**, 1452–1458 (2013) | doi:10.1038/ng.2802





Mol Psychiatry. 2016 Feb; 21(2): 189–197.
Published online 2015 Apr 14. doi: 10.1038/mp.2015.37

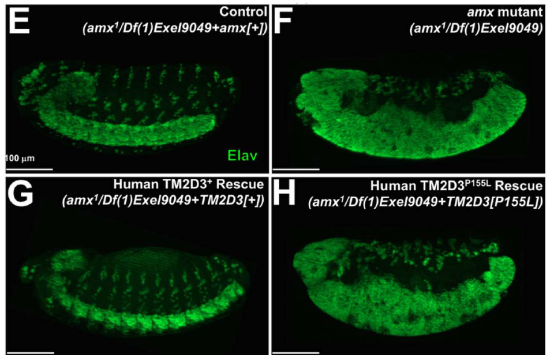
GWAS for executive function and processing speed suggests involvement of the *CADM2* gene

CA Ibrahim-Verbaas[1,2,9], J Bressler[3,9], S Debette[4,5,6,9], M Schuur[1,2,9], AV Smith[7,8,9], JC Bis[9], G Davies[10,9], S Trompet[11,12], JA Smith[13], C Wolf[14], LB Ghanbari[15], Y Liu[16], V Vitart[17], M Kirin[18], K Petrovic[19], O Polasek[20], L Zgaga[21], C Fawns-Ritchie[10], P Hoffmann[22,23,24], J Karjalainen[25], J Lahti[26,27], DJ Llewellyn[28], IO Schmidt[29], KA

- Joint NIA/NHGRI project
- CHARGE and ADGC consortia
- Two funded groups at BU
  - Sudha Seshadri (PI U01)
  - Lindsay Farrer (BU PI U19)
- Three phases
- ~10,000 WES
- ~10,000 WGS
  - Case/control analyses
  - Family based
  - Endophenotypes
- *OPRL1*
- *GAS2L2*

Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium

- Framingham Heart Study



PLoS Genet. 2016 Oct 20;12(10):e1006327. doi: 10.1371/journal.pgen.1006327. eCollection 2016.

Rare Functional Variant in TM2D3 is Associated with Late-Onset Alzheimer's Disease.

Jakobsdottir J[1], van der Lee SJ[2], Bis JC[3], Chouraki V[4,5], Li-Kroeger D[6,7], Yamamoto S[6,7,8], Grove ML[9], Naj A[10], Vronskaya M[11], Salazar JL[6], DeStefano AL[5,12], Brody JA[3], Smith AV[1,13], Amin N[2], Sims R[11], Ibrahim-Verbaas CA[2,14], Choi SH[5,12], Satizabal CL[4,5], Lopez OL[15], Beiser A[4,5,12], Ikram MA[2,14,16], Garcia ME[17], Hayward C[18,19], Varga TV[20], Ripatti S[21,22], Franks PW[20,23,24], Hallmans G[25], Rolandsson O[26], Jansson JH[23,27], Porteous DJ[19,28], Salomaa V[29], Eiriksdottir G[1], Rice KM[30], Bellen HJ[6,7,8,31], Levy D[5,32,4], Uitterlinden AG[2,33], Emilsson V[1,34], Rotter JI[35], Aspelund T[1,36]; Cohorts for Heart and Aging Research in Genomic Epidemiology consortium; Alzheimer's Disease Genetic Consortium; Genetic and Environmental Risk in Alzheimer's Disease consortium, O'Donnell CJ[5,32], Fitzpatrick AL[37,38], Launer LJ[17], Hofman A[2], Wang LS[39], Williams J[11], Schellenberg GD[39], Boerwinkle E[9,40], Psaty BM[3,37,41,42], Seshadri S[4,5], Shulman JM[6,7,8], Gudnason V[1,13], van Duijn CM[2].

Mechanisms of Neurodegeneration: Prion and Alzheimer's Diseases

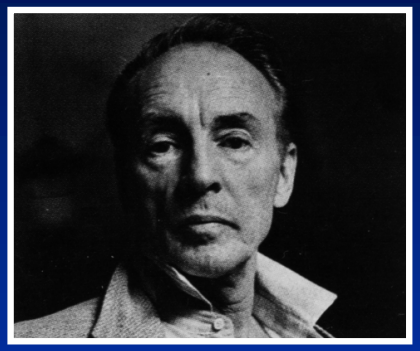
David A. Harris

Chair and Professor

Biochemistry
MED

BOSTON UNIVERSITY

PRION DISEASES: Infectious neurological disorders



Creutzfeldt-Jakob Disease

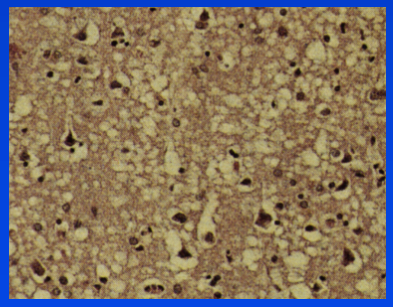
Kuru

Mad Cow Disease (BSE)

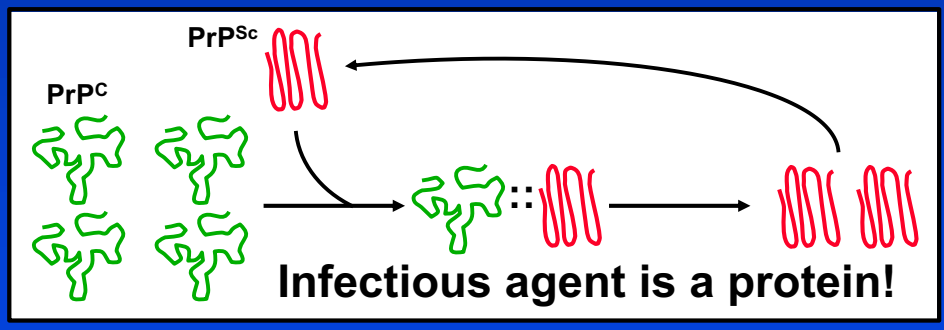
Clinical Features

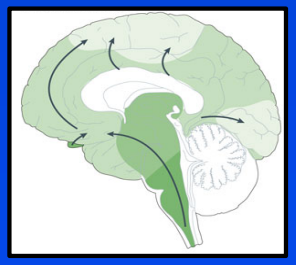
- Dementia
- Ataxia, tremor, myoclonus
- Incubation: years
- Fatal

Neuropathology

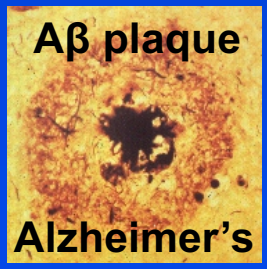


Spongiosis



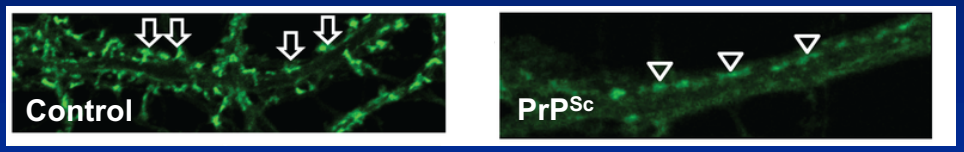


Prion-like spread In AD, PD, etc.

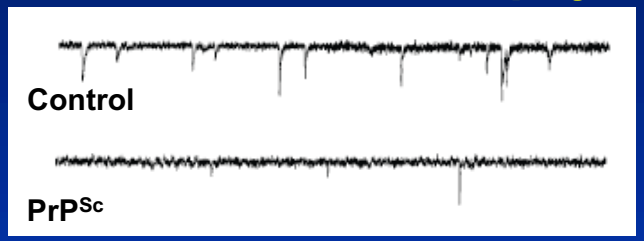


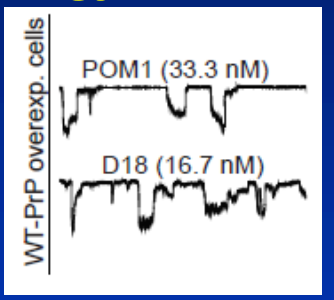
HARRIS LAB: How do prions and Aβ cause neurodegeneration?

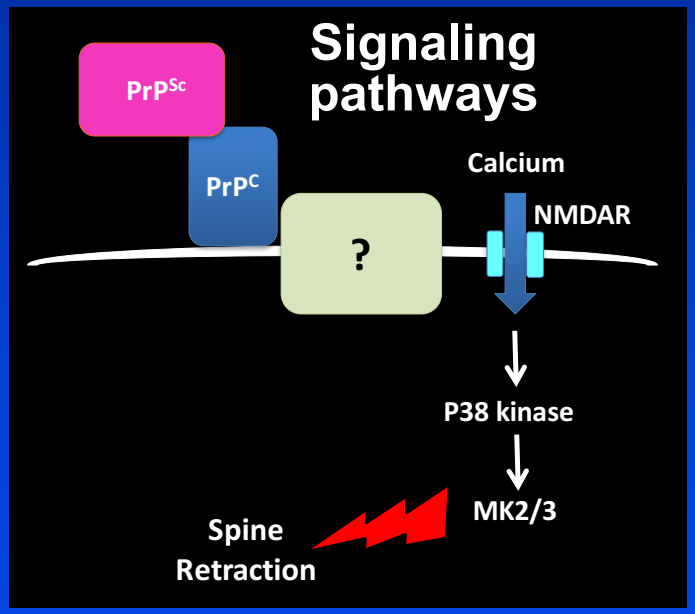
PrP^{Sc} and Aβ are synaptotoxic

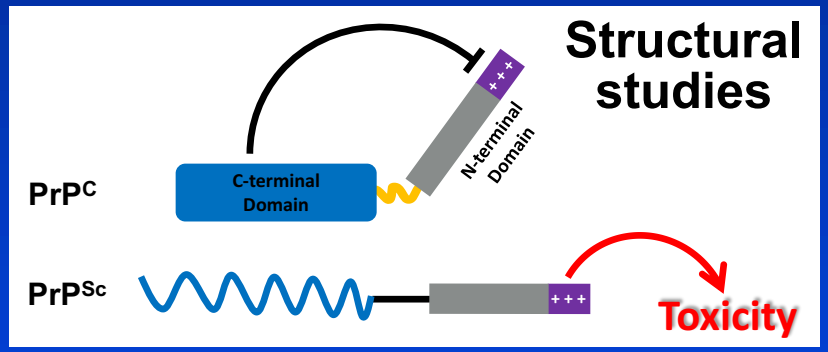


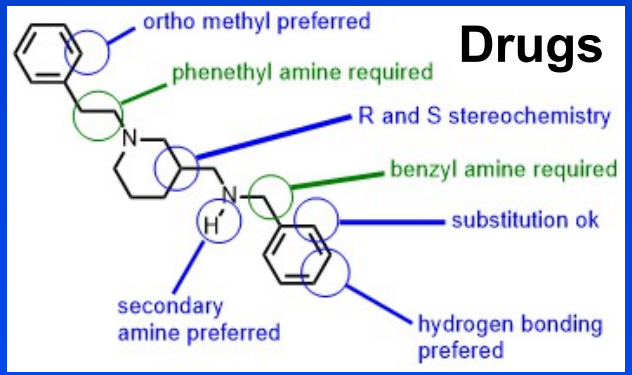
Electrophysiology



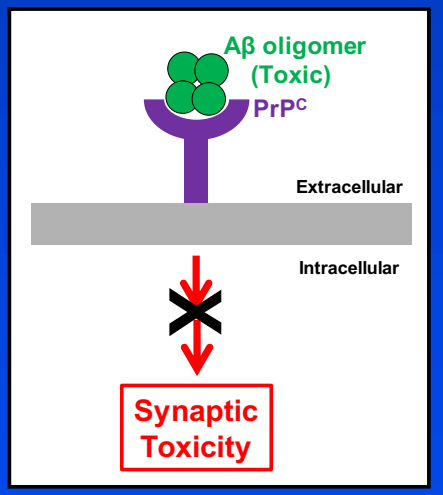








PrP^{C} as an Aβ receptor in AD



Molecular and Synaptic Mechanisms Underlying Neurodevelopmental and Neurodegenerative Disorders

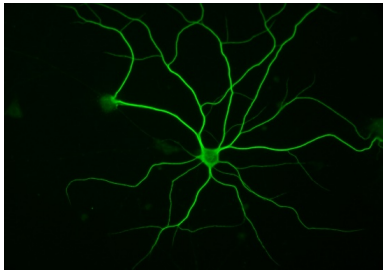
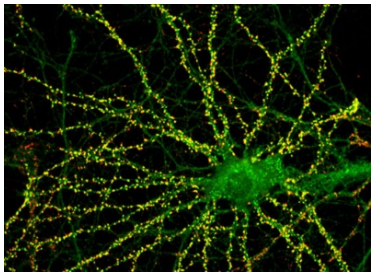
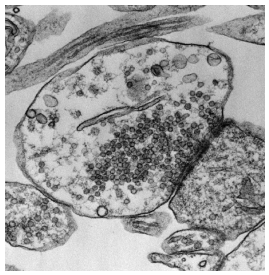
Angela Ho

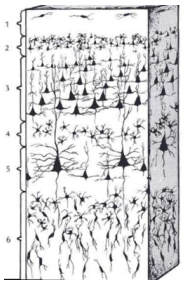
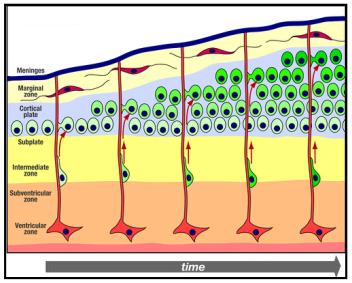
Associate Professor

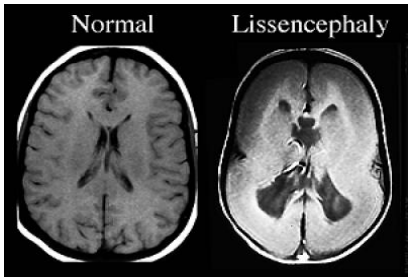
Biology
CAS

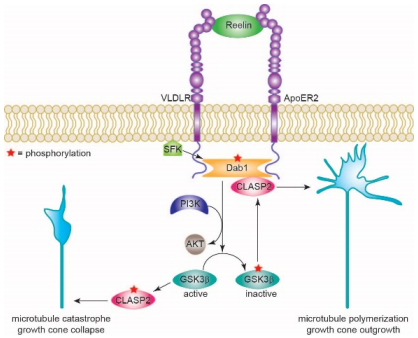
BOSTON UNIVERSITY

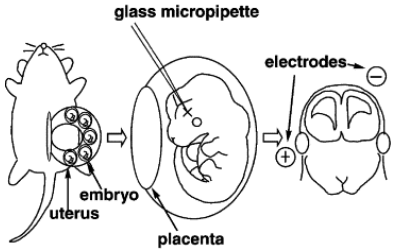
How does the brain develop?

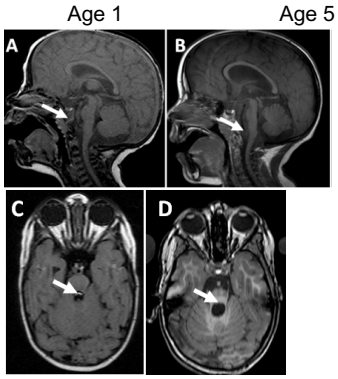






Beffert et al., 2012, *J Neurosci*
Dillon et al., 2017, *Neuron*
Funded R21 MH100581 2013-2016

Undiagnosed Diseases Network
NHGRI, NIH, ORDR

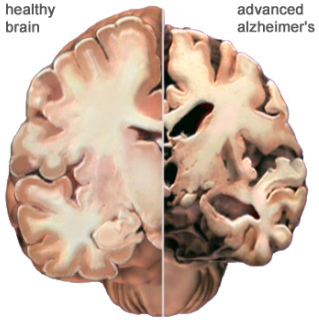


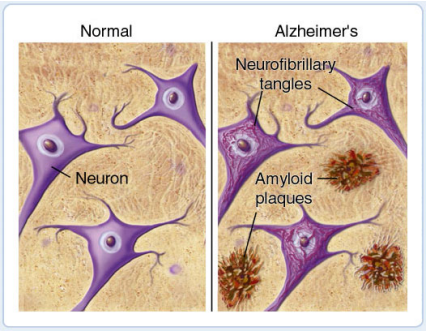
microcephaly
progressive brain atrophy global developmental delay

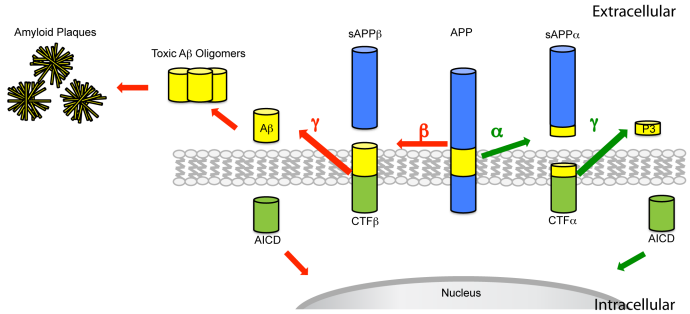
The FOX family play roles in determining cell proliferation and cell fate specification during early development

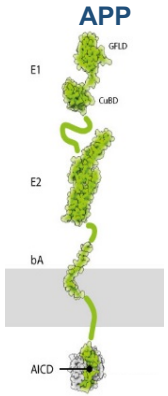
Funded R21 GM114629 2015-2017

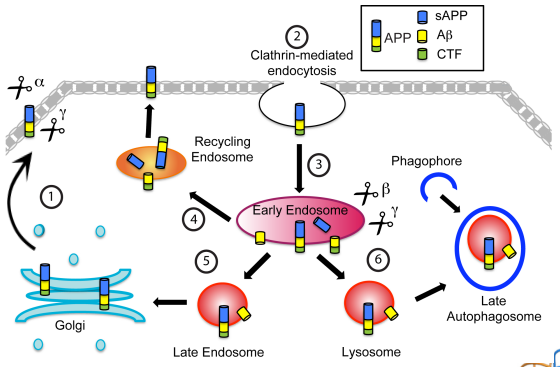
What causes Alzheimer's disease?

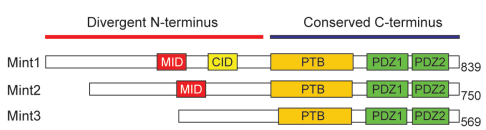


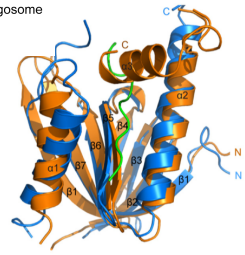




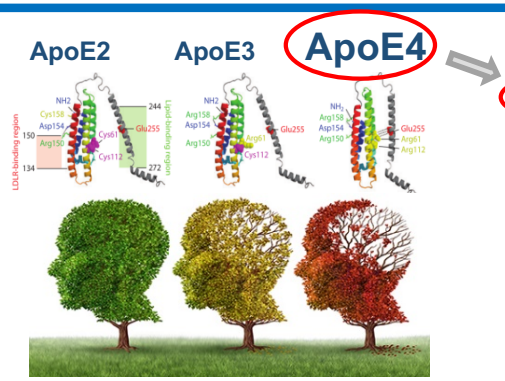




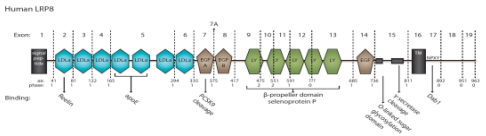


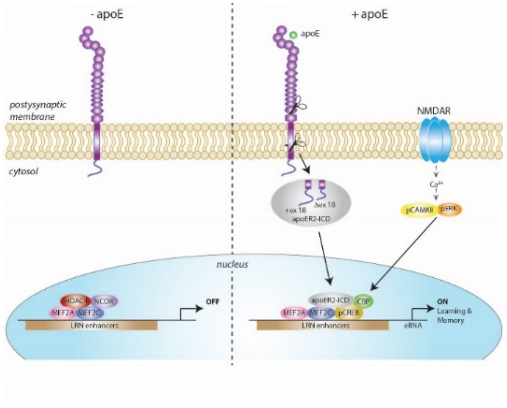


Matos et al., 2012, *PNAS*
Chaufty et al., 2012, *J Neurosci*
Sullivan et al., 2014, *JBC*
Funded R01 AG044499 2014-2019



Strongest genetic risk factor associated with late-onset AD





Harold and Margaret Southerland Alzheimer's Research Fund
R01 AG057649 - *pending*

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MicroRNA-Based Biomarkers in Neurodegenerative Disease

Adam Labadorf

Director, BU Bioinformatics Hub, Bioinformatics Program, and
Research Scientist, Neurogenetics Lab, Neurology, MED

Boston University Office of the Vice President and Associate Provost for Research

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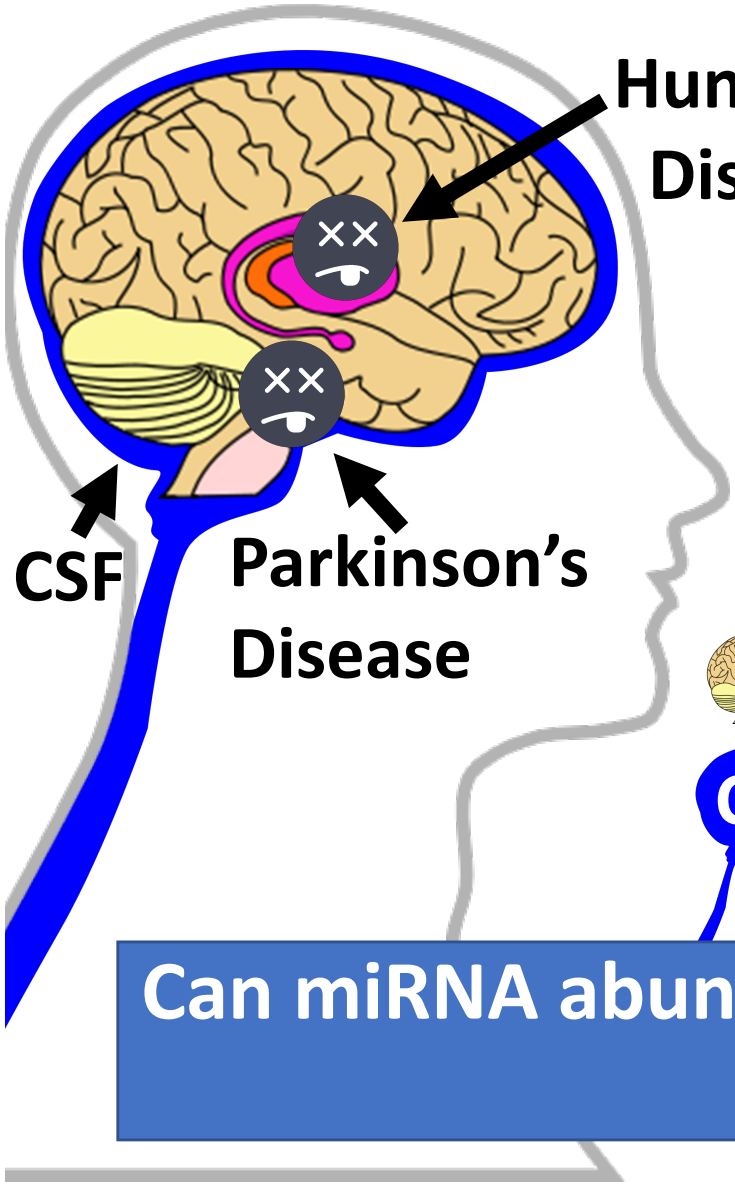
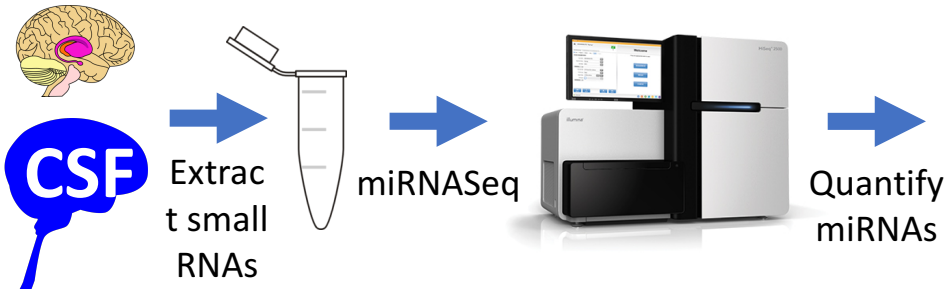
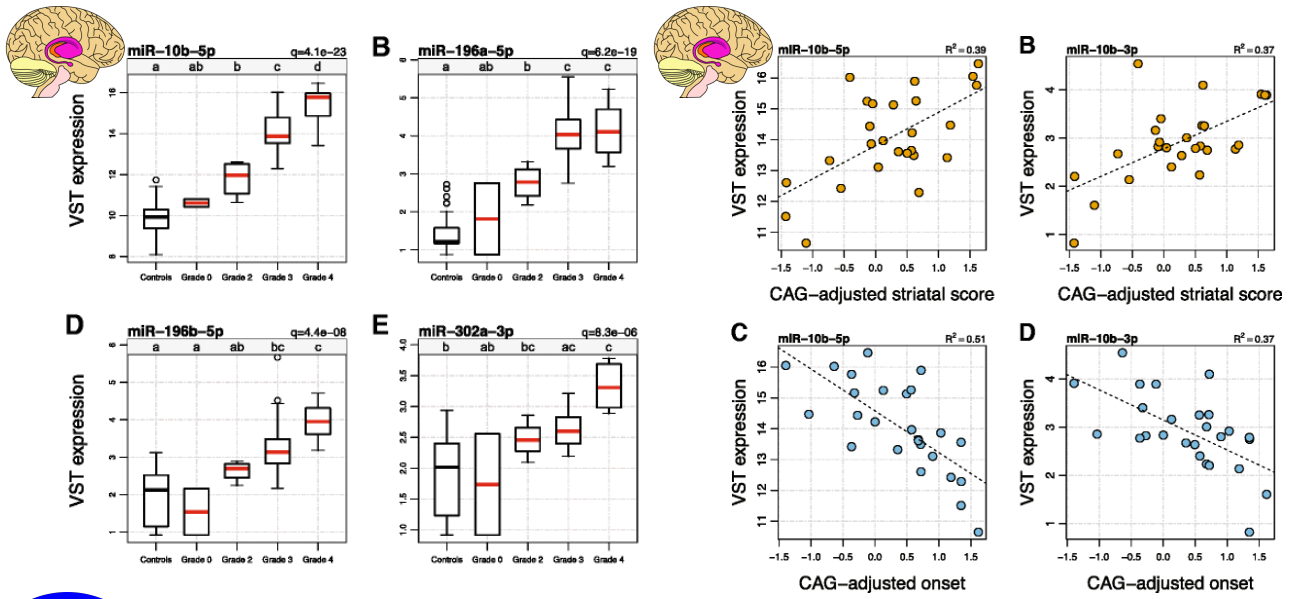


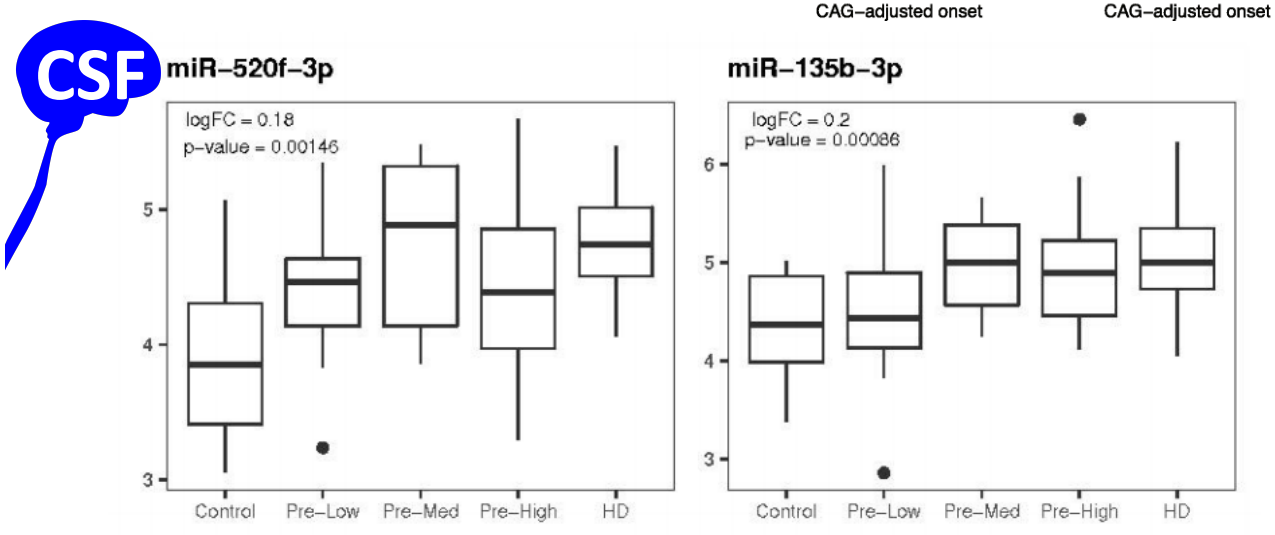
The Data:

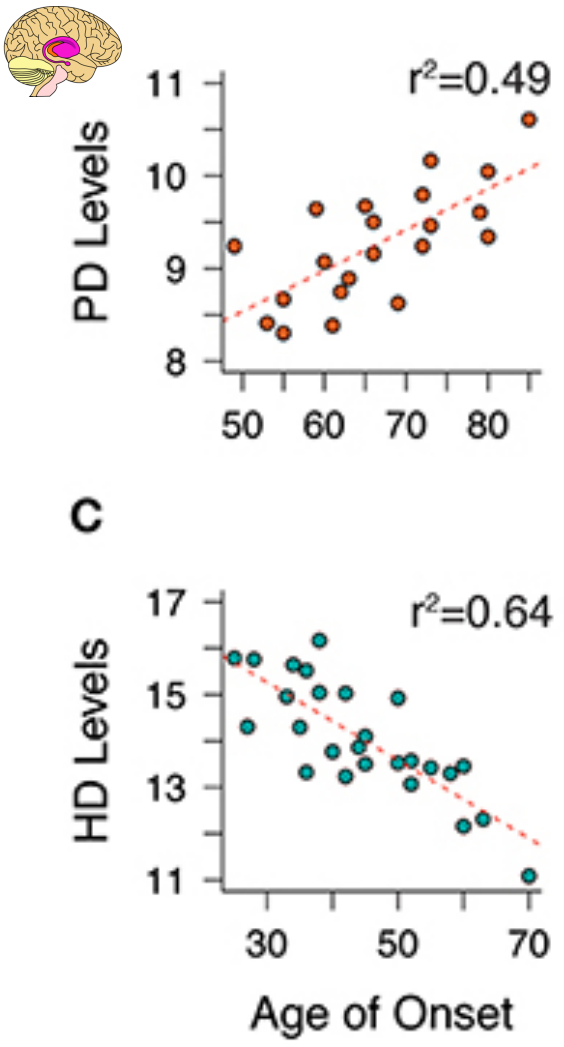


Correlation with disease features

Can miRNA abundance be used as a biomarker for HD and PD?


miR−10b−5p
q=4.1e−23
a ab b c d
VST expression
Controls Grade 0 Grade 2 Grade 3 Grade 4
B
miR−196a−5p
q=6.2e−19
a ab b c c
D
miR−196b−5p
q=4.4e−08
a a ab bc c
E
miR−302a−3p
q=8.3e−06
b ab bc ac c
miR−10b−5p
R² = 0.39
CAG−adjusted striatal score
B
miR−10b−3p
R² = 0.37
CAG−adjusted striatal score
C
miR−10b−5p
R² = 0.51
CAG−adjusted onset
D
miR−10b−3p
R² = 0.37
CAG−adjusted onset


CSF
miR−520f−3p
logFC = 0.18
p−value = 0.00146
miR−135b−3p
logFC = 0.2
p−value = 0.00086
Control Pre−Low Pre−Med Pre−High HD


PD Levels
r²=0.49
C
HD Levels
r²=0.64
Age of Onset

Regulation of Emotional States

Helen Barbas

Professor

Health Sciences, SAR, and
Anatomy & Neurobiology, MED

Research is supported by NIH grants from NIMH, NINDS, NSF, CELEST, Autism Speaks, and The Brain and Behavior Research Foundation

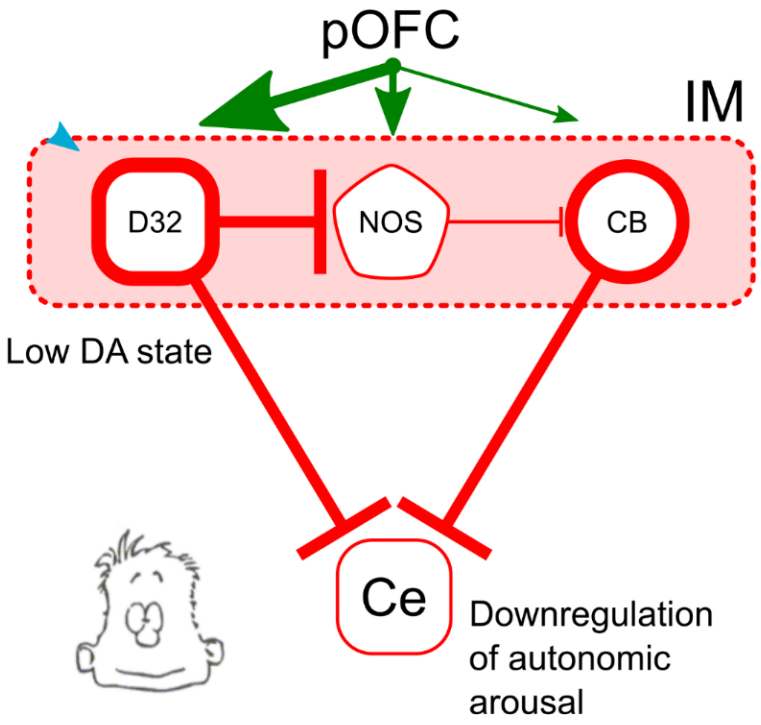
Regulation of emotional states

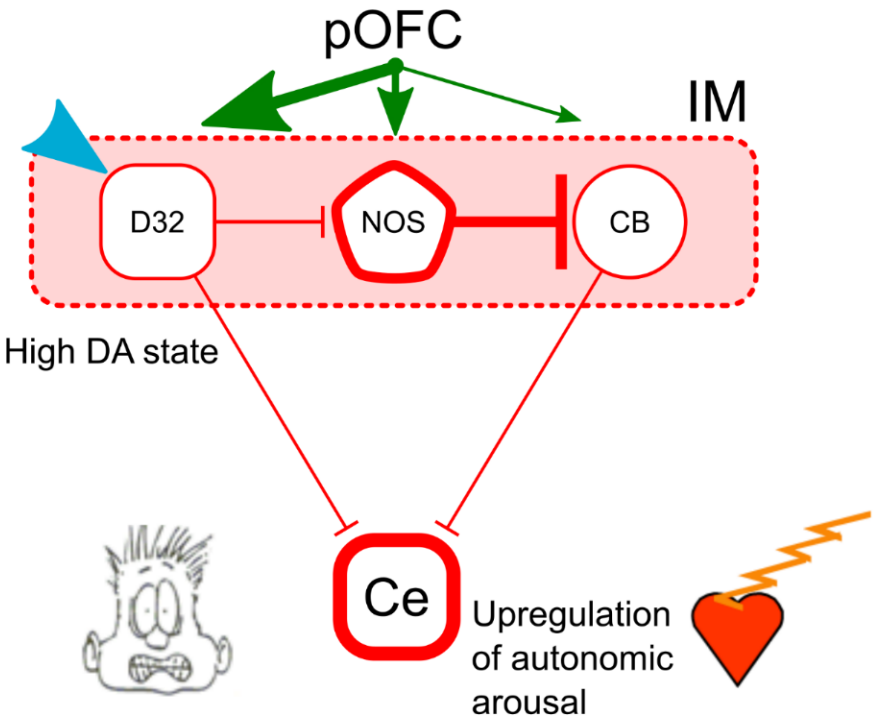
Pathways in the brain that underlie our thoughts and emotions converge on the same areas:

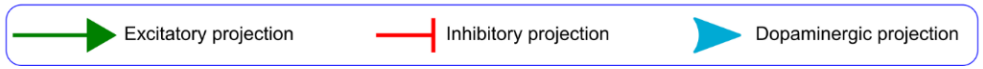
a way for emotions to influence cognition and action

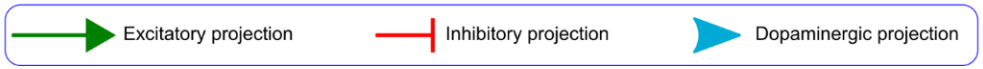
How do we shift from a calm state, to another state to cope with an emergency, or to an abnormal state such as a condition of panic?

We recently discovered a specific innervation by a prefrontal pathway to an inhibitory system in the amygdala, the brain's emotional center. The prefrontal pathway can bias the system by contacting distinct classes of inhibitory neurons to flexibly switch between states. The switch between states is based on the level of the neurotransmitter dopamine in the system.









Adapted from: Neuroscience, 2016; J. Neuroscience, 2017, in press (early release)

Discerning Disease Mechanism From Network Maps

Benjamin Wolozin

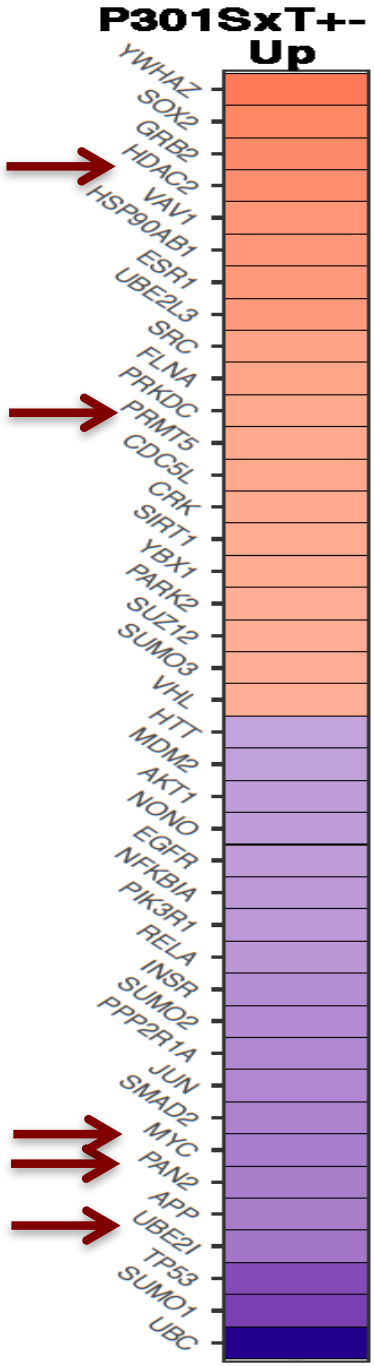
Professor

Pharmacology & Experimental Therapeutics and Neurology
MED

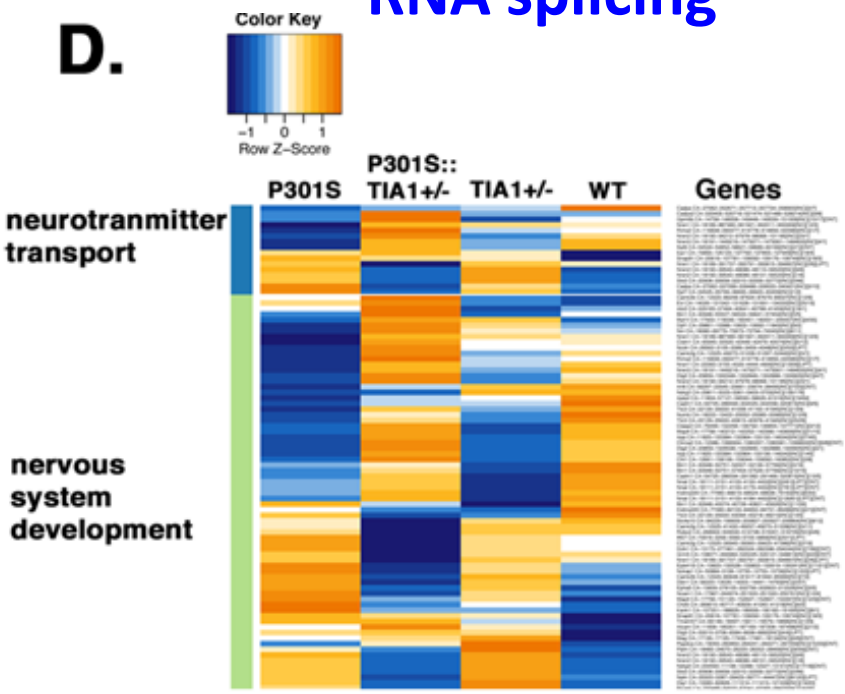
COI: Aquinnah Pharmaceuticals

BOSTON UNIVERSITY

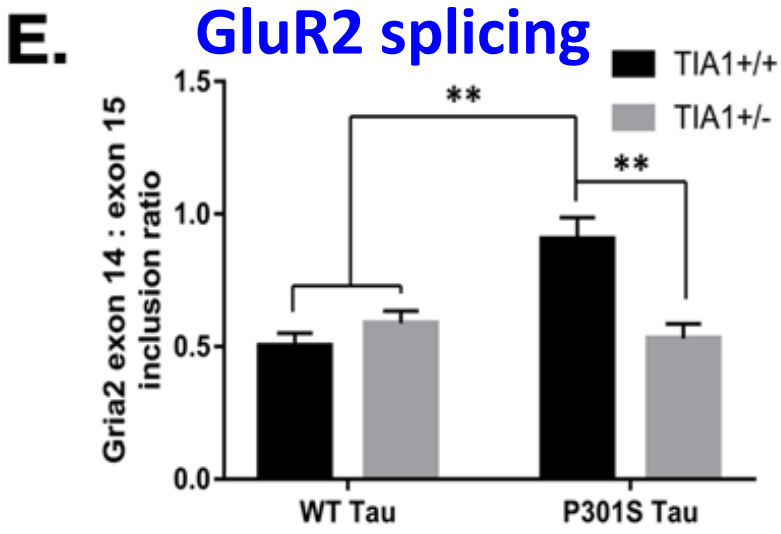
TIA1 reduction protects P301S tau mice: RNAseq



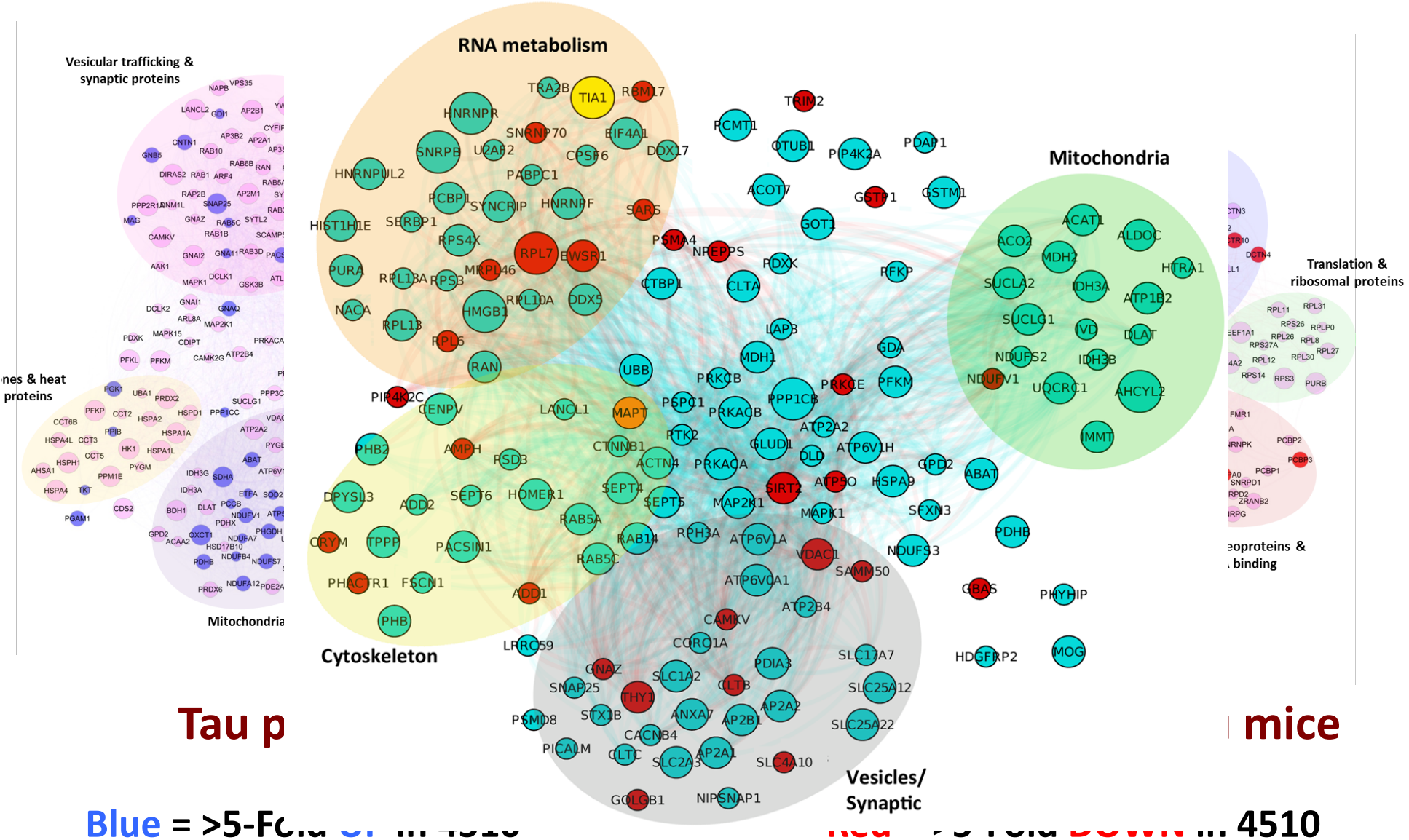
RNA splicing



GluR2 splicing



Proteomic analysis of TIA1 and tau in WT and “AD” mouse models

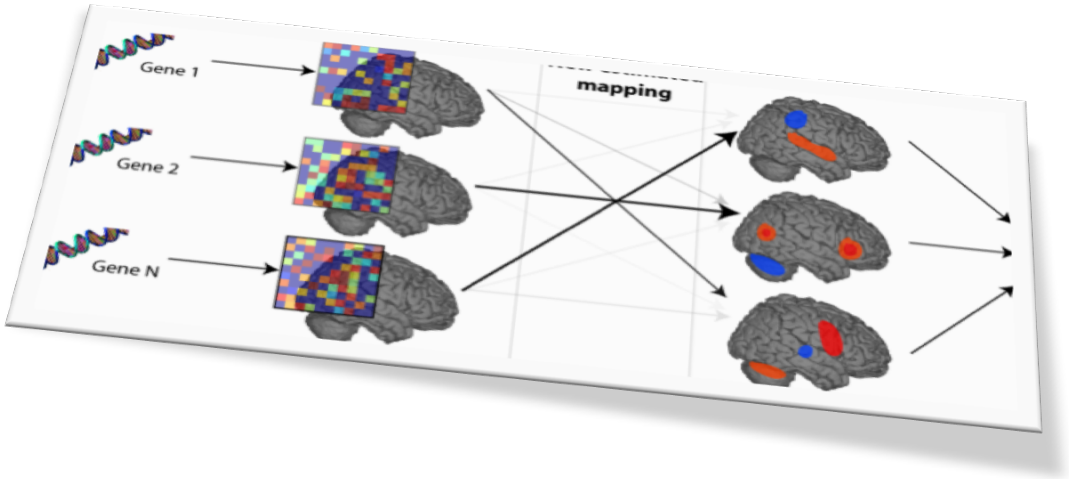


Tau p … mice

Blue = >5-Fold … 4510

TIA1 Network in WT vs. TIA1 KO mice

Gene Expression as an Intermediate Phenotype in Speech and Language Disorders



Jason W. Bohland

Assistant Professor

Health Sciences and
Speech, Language & Hearing
Sciences
SAR

And Emma M. Myers

Boston University Office of the Vice President and Associate Provost for Research

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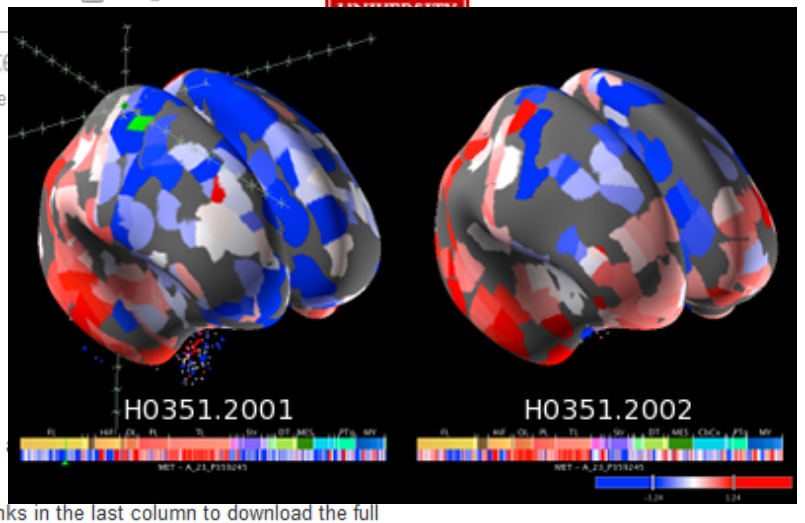
Genes implicated in speech and language disorders

Allen Human Brain Atlas



Search

Home | People (Lab members) | Research (Research areas) | Publications (Articles, etc.) | Resource (Database)

SLDB
Speech/Language Disorders Database

- Genes
- Loci
- Brain Imaging Data
- Suggest an Addition
- Help

Gene / phenotype associations for ROBO1

- Click column headers to sort. Click to expand any row to see more details about the particular variants of ROBO1 and a particular phenotypic variable.
- Click the Pubmed IDs in the last column to link out to the primary research article. Click the links in the last column to download the full *Genotype-Phenotype* record as JSON or XML formatted text.

Entrez Id	Symbol	Location	Disorder	Brief Phenotype	Reference	Year	Download
6091	ROBO1	3p12	Dyslexia	Reduced expression of ROBO1 on chromosomes from dyslexics	Hannula-Jouppi et al	2005	
6091	ROBO1	3p12					
6091	ROBO1	3p12					
6091	ROBO1	3p12					
6091	ROBO1	3p12					

- Dyslexia
- Specific language impairment
- Childhood apraxia of speech
- Persistent developmental stuttering
- Other

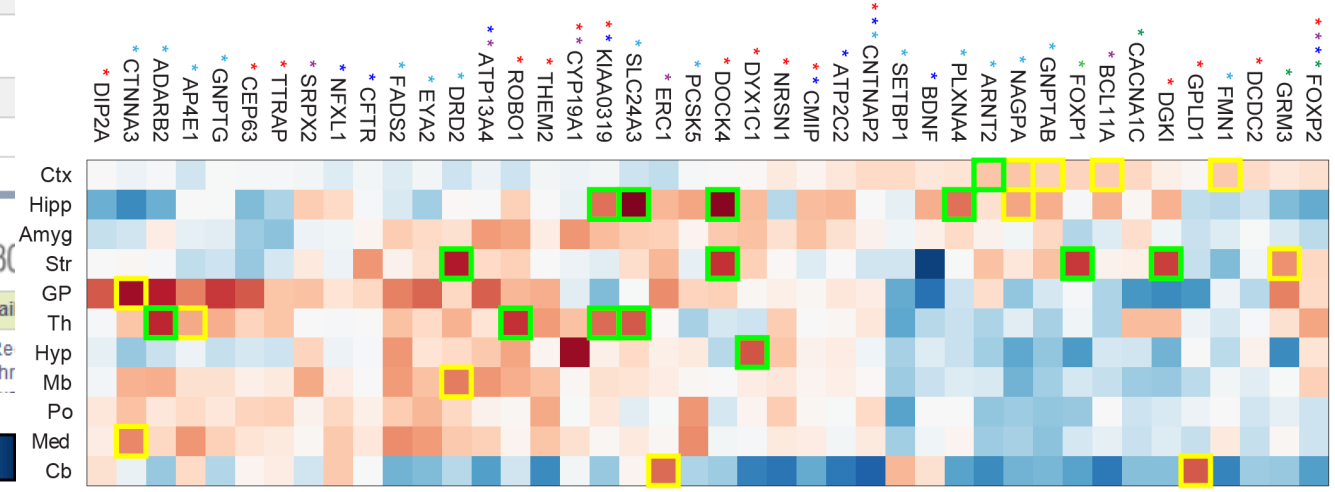
Negative evidence for association with ROBO

Conflicting Ref	Year	Original Report	Fai
Venkatesh et al	2013	Hannula-Jouppi et al (2005)	Re chr

2 1 0 −1 −2

z

Is there convergence in where genes implicated in these disorders are (co)expressed in the brain?



Quantitative Neuroscience Laboratory

BU

Neuroanatomical enrichment

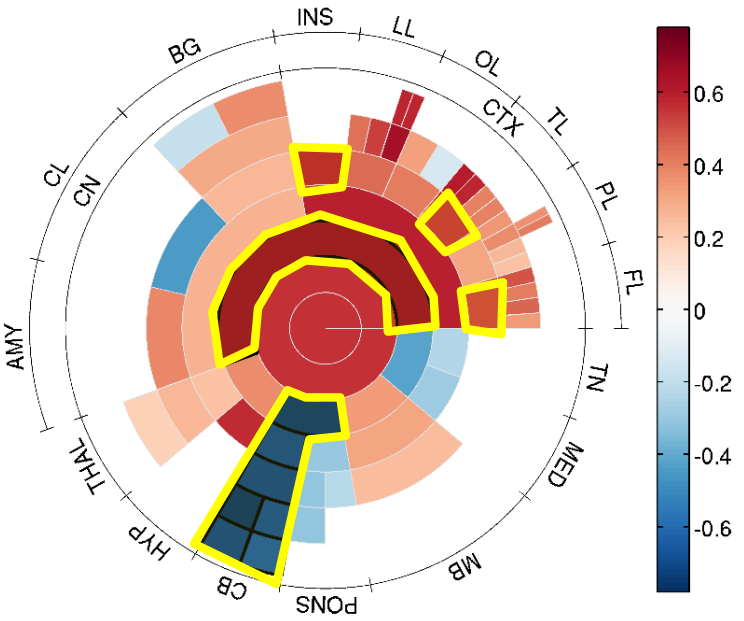
ADARB2	CTNNA3	FOXP1	ROBO1
AP4E1	CYP19A1	FOXP2	SETBP1
ARNT2	DCDC2	GNPTAB	SLC24A3
ATP13A4	DGKI	GNPTG	SRPX2
ATP2C2	DIP2A	GPLD1	THEM2
BCL11A	DOCK4	GRM3	TTRAP
BDNF	DRD2	KIAA0319	
CACNA1C	DYX1C1	NAGPA	
CEP63	ERC1	NFXL1	
CFTR	EYA2	NRSN1	
CMIP	FADS2	PCSK5	
CNTNAP2	FMN1	PLXNA4	

High-confidence "language genes" have enhanced expression in specific areas of the neocortex

Bold outlines indicate significant (P < 0.05, Bonferroni-corrected) enrichment

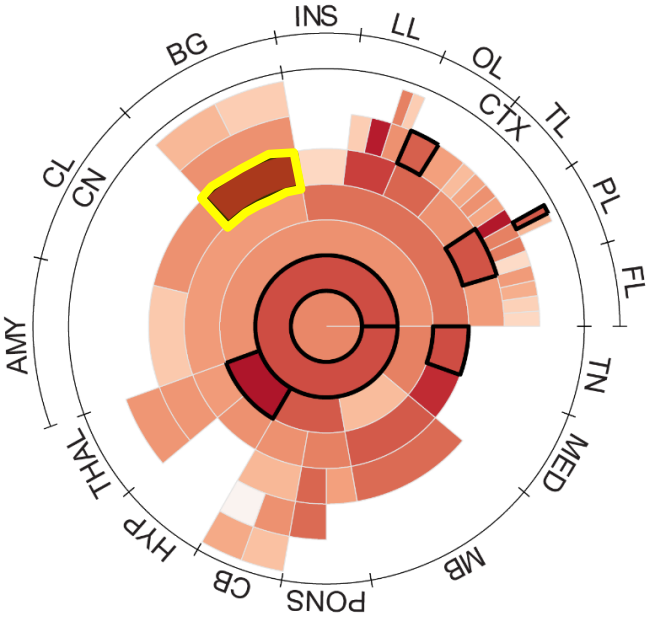
GENE SET ENRICHMENT

HIGH CONFIDENCE GENES

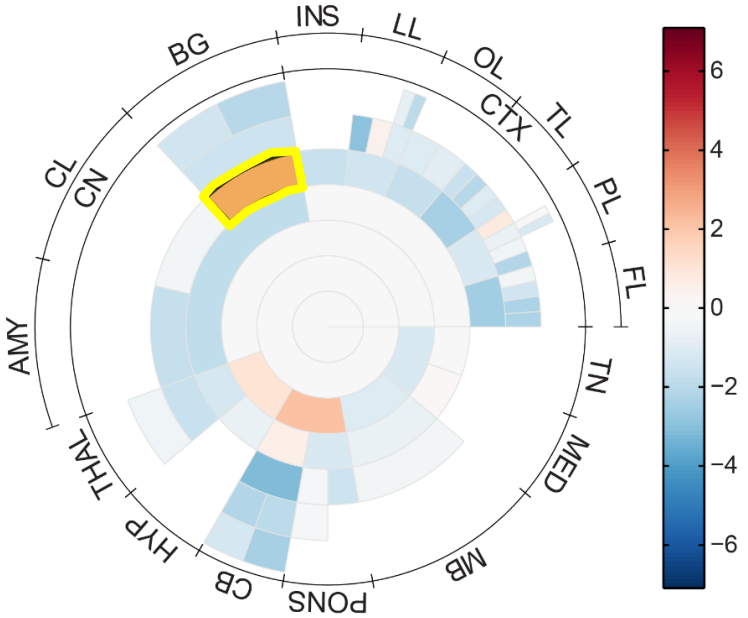


GENE PERMUTATION

STUTTERING CANDIDATES



SAMPLE PERMUTATION



Stuttering associated genes have enhance co-expression in the basal ganglia

Specific to the gene set and the brain region

Quantitative Neuroscience Laboratory

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